REMARKS

Herewith, claims 1-3 and 21-24 are canceled, claims 4-9 and 11-17 are amended, and claims 25-27 are newly presented. Accordingly, pursuant to the entry of the instant amendment, claims 4-17 and 25-27 are presently pending.

In an effort to expedite prosecution and simply the issues at hand, Applicants have herewith canceled claims 1-3 in favor of now independent claim 4, amended to recite "A process for separating a VWF having a high specific VWF activity from a VWF having a low specific VWF activity, said process comprising the steps: (a) binding VWF to a hydroxylapatite column matrix, (c) washing out VWF having a specific VWF activity less than 70 U per mg VWF antigen and (d) eluting a VWF having a specific VWF activity greater than 120 U per mg VWF antigen". Claims 5-9 and 11-7 have been amended to depend from newly independent claim 4 and to include certain minor revisions necessary to preserve consistency and antecedent basis. New claims 25-27 further define the process of claim 4 in terms of certain preferred parameters.

Support for the amendments presented herewith is found in the specification as originally filed, for example in the originally filed claims. Additional support is found at:

- Page 3, lines 19-22: "[A] value of >120 U per mg VWF antigen is referred to as a high specific VWF activity and a value of < 70 U per mg VWF antigen is regarded as a low specific VWF activity";
- Page 5, lines 10-15: "In wash step (b), the hydroxylapatite matrix is washed with a buffer having a medium salt concentration . . . usually 100 to 300 mM, preferably 200 to 300 mM, more preferably 200 to 270 mM"; and
- Page 5, lines 15-18: "In step (c), VWF having a high specific VWF activity can be eluted with a buffer having a relatively high salt concentration . . . usually contains 200 to 500 mM, preferably 250 to 500 mM, more preferably 300 to 400 mM".

Thus, Applicants respectfully submit that no new matter has been added. However, Applicants reiterate that the instant amendments are presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

Turning to the outstanding Office Action of February 4, 2009:

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-17 and 23-24 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner characterizes the relative terms "high activity", "low activity", "high specific activity", "low specific activity", "high specific VWF activity", "low specific VWF activity", and "relatively high salt concentration" as unclear, lacking sufficient metes and bounds.

At the outset, Applicants wish to point out that claims 1-3 and 23-24 have been canceled, thereby rendering moot their rejection above. As for remaining claims 4-17, the fact that a claim includes one or more terms of degree does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. Seattle Box Co., v. Industrial Crating & Packing, Inc., 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Rather, acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. Given that the instant specification provides clear definitions for each of the above-noted terms of degree, Applicants respectfully submit that one of ordinary skill in the art would be reasonably apprised of the scope of the invention.

Nevertheless, in an effort to expedite prosecution, Applicants have canceled the objectionable relative terms from now independent claim 4 in favor of precise parameters (e.g., "specific VWF activity greater than 120 U per mg VWF antigen", "specific VWF activity less than 70 U per mg VWF antigen", and "salt concentration ranging from 200 mM to 500 mM"). Accordingly, Applicants respectfully submit that the claims as amended herewith meet the threshold requirements for clarity and precision set forth in 35 U.S.C. § 112, second paragraph.

As such, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections of claims 4 -17 in view of the amendments and remarks herein.

Rejections under 35 U.S.C. § 102

Claims 21-24 stand rejected under 35 U.S.C. § 102(b) for being anticipated by Burnouf-Radosevich et al. (Vox Sanguinis 1992). Applicants respectfully submit that the cancellation of claims 21-24 renders this rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of thereof.

Claims 1-3, 5, 6, 11, and 21 stand rejected under 35 U.S.C. § 102(b) for being anticipated by Gorman et al. (Thrombosis Research, 1978). Applicants respectfully submit that the cancellation of claims 1-3 and the instant amendment to claim 4 renders this rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of thereof and further petition for the allowance of remaining claims 4-17 and 25-27 in view of the remarks hereinbelow:

VWF molecules are known to be present in solution in different oligomerization states, ranging from dimers to 20-mers. High molecular weight VWF molecules are believed to have a higher specific VWF activity and therefore a higher clinical activity, while low molecular weight VWF molecules (e.g., dimers and tetramers) tend to show a decreased specific VWF activity and less robust clinical use. As noted in the instant specification at page 2, first paragraph, a frequent problem in the production of a VWF preparation is the loss of specific VWF activity. The loss of specific VWF activity correlates structurally with proteolytic degradation reactions that, in turn, lower the content of high-molecular VWF molecules (multimers) and raise the content of low-molecular VWF molecules (dimers/tetramers). The present invention is based on the finding that hydroxylapatite chromatography can advantageously be used for separating VWF molecules of differing quality, i.e., low molecular weight VWF oligomers having lower specific VWF activity and therefore lower clinical activity from high molecular weight VWF oligomers having high specific VWF activity and therefore higher clinical activity.

In the event there is some confusion between the terms "specific activity" and "specific VWF activity", Applicants wish to take this opportunity to clarify the critical distinction. The term "specific activity" generically refers to the activity of a particular protein per total amount of protein in solution and is thus an indicator of the purity of that protein in relation to the absence of different proteins. Thus, the specific activity of a particular protein in solution can be increased through the removal of impurities. In contrast, the phrase "specific VWF activity" refers to the VWF activity per amount of VWF antigen. Thus, the specific VWF activity is an indicator of the quality of the VWF molecules contained in the solution. It is important to note that the specific VWF activity of a particular sample cannot be increased through the simple removal of "impurities".

The process of the present invention provides an easy and efficient means for separating VWF molecules having high specific VWF activity (i.e., greater than 120 U per mg VWF antigen) from those having low specific VWF activity (i.e., less than 70 U per mg VWF antigen). Accordingly, by removing the less active VWF molecules, one can obtain a highly active VWF preparation even from less active starting materials (e.g., a source having a specific VWF activity of less than 100 U per mg VWF antigen).

This stands in stark contrast to the teachings of Gorman. Contrary to the Examiner's suggestion, Gorman does not disclose a process for separating different types of VWF based on their specific VWF activity, more particularly differentiating a VWF having a high specific activity (i.e., greater than 120 U per mg VWF antigen), and presumably a high oligomerization state, from dimeric and tetrameric VWF having a low specific activity (i.e., less than 70 U per mg VWF antigen). Rather, Gorman simply studies the effects of various purification processes (gel-filtration, hydroxylapatite chromatography, SDS-PAGE) on the structure and subunit composition of human anti-haemophilic factor (Factor VIII), more particularly the Factor VIII subunits having Factor VIII coagulant activity (Factor VIIIc), Factor VIII related antigen activity (VIII R-ag or "VWF") and ristocetin cofactor activity. To that end, Gorman discloses that hydroxylapatite chromatography of gel-filtered Factor VIII-containing samples resulted in the simultaneous elution of all three factors together as a single peak (see abstract and Figure 2). Moreover, according to Gorman, HA chromatography results in "no separation of VIIIc from

VIII R-Ag" (see p. 344, emphasis added). Thus, the Gorman reference not only fails to disclose or suggest the use of HA chromatography to separate VWF (VIII R-ag) from other Factor VIII components, such as Factor VIIIc, and in fact suggests the exact opposite, but further fails to disclose or suggest the use of HA to distinguish one type of VWF (i.e., one having a high oligomeric state and thus a high specific VWF activity) from another (i.e., one having a low oligomeric state and thus a low specific VWF activity).

It is well settled that a reference must disclose each and every element of a pending claim in order to anticipate. As noted above, Applicants respectfully submit that Gorman fails to disclose or suggest separating VWF molecules of differing specific activity to give rise to a VWF composition having a specific VWF activity of greater than 120 U per mg VWF antigen. Accordingly, in that Gorman neither discloses nor fairly suggests the binding, washing out and eluting steps required by claim 4, it cannot serve to anticipate or render obvious the invention of pending claims 4-17 and 25-27. As such, Applicants respectfully request reconsideration and withdrawal of outstanding rejections and further petition for the allowance of claims 4-17 and 25-27 in view of the amendment and remarks herein.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that claims 4-17 and 25-27 are in condition for allowance and respectfully petition for the early issuance of a Notice of Allowance confirming such.

The Office Action of **February 4, 2009** set a three-month shortened statutory period for response, response falling due **May 4, 2009**. Pursuant to the entry of the petition for one-month extension of time file concurrently herewith, this deadline is extended to **June 4, 2009**. Accordingly, Applicants submit that this response is timely and no additional fees, apart from those included herewith, are required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

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